Just the Facts: Adverse events associated with immune checkpoint inhibitor treatment for cancer

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CLINICAL SCENARIO

A 64-year-old male with lung cancer presents to the emergency department with one week of cough and increasing shortness of breath. At triage, his temperature is 37.3° Celsius, heart rate 106 beats per minute, blood pressure 136/80, and oxygen saturation 87% on room air, which improves to 94% with 3 L of oxygen via nasal prongs. He has a chest X-ray that demonstrates bilateral patchy infiltrates. He is treated for pneumonia with antibiotics. His respiratory status worsens, with an increasing oxygen requirement. Additional history reveals that the patient recently finished treatment for lung cancer with an immune checkpoint inhibitor.

KEY CLINICAL QUESTIONS

1. What is cancer immunotherapy?

Novel cancer immunotherapies are increasingly being used in the management of many malignancies. Immunotherapy modifies the immune response, allowing the immune system to recognize and destroy cancer cells.[1,2] Immunotherapy can be passive or active. Examples of passive immunotherapies include tumor-specific monoclonal antibodies (i.e., trastuzumab), cytokines (i.e., interferon-alpha, interleukins), and adoptive cell transfer (i.e., chimeric antigen receptor [CAR] T-cell therapy).[2] Active immunotherapies include vaccines, viruses, and immune checkpoint inhibitors.[2]

The immune system has multiple "checkpoints" that modulate the immune response. These checkpoints involve proteins on the surfaces of either the T-cell (CTLA-4 and PD-1) or the antigen presenting cell, such as a cancer cell (PD-L1) that, when engaged, can lead to T-cell inhibition.[1] Immune checkpoint inhibitors target these proteins leading to increased T-cell activity, allowing the immune system to destroy cancer cells.[3] Immune checkpoint inhibitor classes include CTLA-4 inhibitors (ipilimumab), PD-1 inhibitors (nivolumab, pembrolizumab), and PD-L1 inhibitors (atezolizumab, avelumab, durvalumab). These drugs have shown benefit in treating various malignancies, such as melanoma, renal cell carcinoma, lung cancer, and some hematological malignancies.[3] While the majority of immune checkpoint inhibitors are used for advanced and/or metastatic cancers, use of these treatments in the earlier stage of disease is an active area of research. In the United States in 2018, it was estimated that over 40% of cancer patients were eligible for checkpoint inhibitor immunotherapy.[4] Given the increasing use of immune checkpoint inhibitors, this article will focus on these therapies.

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2. What types of adverse events occur with immune checkpoint inhibitor treatment?

Blocking immune checkpoints with immune checkpoint inhibitors promotes anti-tumor immunity; however, this can overstimulate the immune system against the host, leading to adverse events related to autoimmune toxicity. These adverse events are known as *immune-related adverse events*. Immune-related adverse events are common in patients treated with an immune checkpoint inhibitor, with reports of up to 50% of patients on nivolumab experiencing an adverse event.[1,3] Mild-to-moderate adverse events are more common than severe events; however, some adverse events can be potentially life-threatening (< 1% of cases).[1] The use of a combination of immune checkpoint inhibitors is associated with higher rates of significant toxicity.[1]

Immune-related adverse events can affect any organ system or multiple systems simultaneously. The most common immune-related adverse events involve the skin and gastrointestinal tract.[1,3] See Table 1 for some organ-based adverse events reported with immune checkpoint inhibitor use.[1,3,5]

3. When do immune-related adverse events occur in patients who have been treated with immune checkpoint inhibitors?

The majority of immune-related adverse events occur within 3 to 6 months of starting treatment with immune checkpoint inhibitors. However, some immune-related adverse events can occur as early as weeks following initiation of treatment, which is more commonly seen with dual agents.[6] Some immune-related adverse events have been reported to occur up to one year after starting treatment and even months after treatment has been discontinued.[3] Therefore, it is important to obtain a thorough patient history, including details of previous treatments received.

4. How are immune-related adverse events associated with immune checkpoint inhibitor treatment managed?

Immune-related adverse events associated with immune checkpoint inhibitor treatment are typically managed according to the organ system affected and the Common Terminology Criteria for Adverse Events (CTCAE) severity grade.[3,5] Cancer Care Ontario has an approach to grading and management of organ-specific adverse events associated with these treatments, which is available for reference at https://www.cancercareontario.ca/en/guidelines-advice/modality/immunotherapy/immune-therapy-toolkit.

It is essential to consider and rule out alternative causes of the clinical syndrome that may be presenting. For instance, in a patient with possible pneumonitis, pulmonary infection (including atypical infections) should be considered. Following this, if an immune-related adverse event is felt to be the most likely cause of the clinical presentation, corticosteroids are generally used as first-line treatment for most moderate-to-severe immune checkpoint inhibitor-associated, immune-related adverse events.[1,3,5] However, there should be a close collaboration with oncology colleagues regarding the decision to initiate steroids, the dose, and duration of steroids and steroid tapering. Some mild adverse events may only require observation as an outpatient. Some dermatological adverse events may be treated with topical corticosteroids. Other adverse events will require oral steroids (doses can range between 0.5 to 2 mg/kg of prednisone) or intravenous steroids (doses may range between 1 to 2 mg/kg of methylprednisone).[1,5] In patients where there is a high suspicion of severe Grade 3 to 4 immune-related adverse events, or who are unstable, high dose corticosteroids should be considered early and possibly concurrently with empiric coverage for alternative diagnoses with early referral to the appropriate specialists.[3]

Patients with immune-related adverse events that are steroid-refractory may require other immunosuppressants, such as tumor necrosis factor (TNF) alpha inhibitors, azathioprine, or mycophenolate mofetil.[3]

Table 1. Organ-based immune-related adverse events associated with immune checkpoint inhibitor treatment[1,3,5]

Organ system	Common side effects	Rare or serious side effects
Cardiac (< 1%)		Cardiomyopathy
		Pericarditis, myocarditis
Endocrine (5%–20%)	Thyroid dysfunction (hyperthyroid or hypothyroid)	Adrenal insufficiency
		Hypophysitis (i.e., pituitary inflammation)*
Eye/ocular (< 1%)		Conjunctivitis
		Episcleritis
		Uveitis
		Orbital inflammation
Gastrointestinal (1%–30%)	Diarrhea (up to 30%)	Enteritis
	Colitis	
	Hepatitis/transaminitis (1–10%)	
Lung (< 5%)		Pneumonitis
Musculoskeletal (1%–10%)	Arthralgias, myalgias	Myositis
Neurological (< 5%)	Neuropathy	Guillain-Barre syndrome
		Myasthenia gravis
		Aseptic or lymphocytic meningitis
Renal (< 5%)		Nephritis
		Renal failure
Pancreatic (rare)		New-onset diabetes
		Pancreatitis
Skin/mucosal (20%–40%)	Rash/erythema	Toxic epidermal necrosis
	Vitiligo	Stevens-Johnson syndrome
	Dry mouth	

Note: *May present as headache and fatigue and can lead to insufficiency of any pituitary hormones.

5. What are the treatment implications for a patient who has an immune-related adverse event to immune checkpoint inhibitor therapy?

It is unclear whether steroids for the management of immune-related adverse events impact the anti-tumor activity of immune checkpoint inhibitors in the long term.[3] The majority of immune-related adverse events associated with these treatments are thought to be reversible with early steroids at the appropriate dose.[3] However, some adverse events may be permanent. In patients where there is concern of an immune checkpoint inhibitor-associated adverse event, it is important to consult oncology colleagues. Ideally, there should be discussion with the patient's own oncologist because the patient may be required to temporarily suspend immunotherapy and, in cases of severe immune-related adverse events, may be required to discontinue the treatment permanently. In severe immune-related adverse events, the appropriate organ specialist should be involved early on, along with critical care colleagues. If patients develop a severe immune-related adverse event, they will likely not be candidates for ongoing treatment with that particular immune checkpoint inhibitor.

CASE RESOLUTION

A CT scan of the chest shows bilateral patchy nodular infiltrates and no pulmonary embolism. Given the history of immune checkpoint inhibitor treatment, pneumonitis (an immune-related adverse event) is considered. After discussion with oncology and ICU colleagues, intravenous methylprednisone at a dose of 1 mg/kg is started and the patient is admitted to the hospital.

KEY POINTS

Cancer immunotherapy with immune checkpoint inhibitors is increasing.

Immune checkpoint inhibitor treatment may be associated with immune-related adverse events that can affect any organ system.

Most immune-related adverse events occur within 3 to 6 months of starting treatment with immune checkpoint inhibitors. However, some immune-related adverse events can present in a delayed fashion after treatment is completed.

Skin and gastrointestinal adverse events are the most common immune-related adverse events associated with immune checkpoint inhibitor treatment.

Immune-related adverse events are managed according to organ-specific grading. See Cancer Care Ontario's immunotherapy toolkit for healthcare providers for organ-specific immune-related adverse event grading and management guidelines, available at https://www.cancercareontario.ca/en/guidelines-advice/modality/immunotherapy/immune-therapy-toolkit.

Typical first-line treatment for most immune-related adverse events is steroids, which should be considered in collaboration with oncology colleagues.

GLOSSARY OF TERMS

CT: computed tomography
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
ICU: intensive care unit
PD-1: programmed cell death protein 1
PD-L1: programmed death ligand 1

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